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(54) Title: SITE–SPECIFIC CONTROLLED RELEASE DOSAGE FORMULATION FOR MESALAMINE

(57) Abstract

Pharmaceutical formulation for the site–specific delivery of mesalamine in the colon is disclosed. The formulation includes (a) a core comprising mesalamine in an amount effective to produce a therapeutic anti–inflammatory effect; (b) a swellable polymeric coating layer substantially surrounding the core which inhibits the release of mesalamine for a predetermined period of time dependent upon the thickness of the swellable polymeric coating layer, and (c) an outer enteric coating layer substantially surrounding the swellable polymeric coating layer. Methods of achieving the site–specific delivery of mesalamine in the colon are also disclosed.

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SITE-SPECIFIC CONTROLLED RELEASE DOSAGE FORMULATION FOR MESALAMINE

Field of the Invention

The present invention relates to controlled release dosage formulations. More particularly, the present invention relates to site-specific controlled release dosage formulations.

Background of the Invention

Mesalamine, also commonly known as "mesalazine," "5-amino salicylic acid", and "5-ASA", is well known for its anti-inflammatory properties. It is classified a non-steroidal anti-inflammatory drug (N-SAID). Mesalamine has been approved for the treatment of mildly to moderately active ulcerative colitis.

With regard to the action of mesalamine in the treatment of ulcerative colitis and other inflammatory bowel diseases, there exists clear

evidence that i) the effect of mesalamine for treatment of inflammatory bowel diseases is exerted through a local rather than systemic action; and ii) the larger the systemic absorption the higher the possibility of side-effects (including renal necrosis, and pyuria). It is therefore advantageous to achieve maximum mesalamine concentration at the site of the disease, with the smallest possible systemic absorption. Since early release in the small bowel increases the systemic absorption and reduces the drug available for the topical action in the colon, the most powerful system is a technology which completely releases the active principle in the colon.

For this reason, attempts have been made to formulate mesalamine in a manner which will permit the delivery of the drug in the colon, i.e., at the site of the disease, to maximize the therapeutic effectiveness of the drug. Delivery directly in the colon requires formulations which are capable of passing over the entire tract of the small intestine, including the duodenum, jejunum, and ileum, so that the active ingredients are released directly in the colon. Such formulations typically employ coatings for the purpose of preserving the integrity of the formulation while passing through the gastric tract. The high acidity, and presence of proteolytic and other enzymes generates a highly digestive environment which readily dissolves pharmaceutical formulations which do not possess some type of gastro-resistance protection.

Several formulations of mesalamine for delivery in the colon have been proposed. One approved mesalamine formulation is commercially available from Proctor & Gamble Pharmaceuticals under the trade name ASACOL® delayed release tablets. The formulation includes a tablet of mesalamine coated with the commercially available enteric coating EUDRAGIT®-S, which is a methacrylic acid copolymer which dissolves at pH 7 or greater.

Another formulation for mesalamine is commercially available from Marion Merrell Dow under the trade name PENTASA®, based on U.S. Patent Nos. 4,496,553 and 4,908,173 to both Halskov. The formulation includes a tablet formed from a granulate of mesalamine and

polyvinylpyrrolidone prepared using an organic solvent, which granulate is coated prior to the formation of the tablet, with a cellulose derivative coating material that will gradually release the active.

Solvay provides two formulations of mesalamine under the trade name ROWASA®. The formulations include a rectal suppository formulation and a rectal suspension enema.

In addition to the foregoing formulations, European Patent No. 366,621 describes a formulation for selective colon delivery of various drugs including ketoprofen and ibuprofen. The formulation includes a core coated with three different layers: an inner layer including an anionic polymer, an outer gastro-resistant layer and in intermediate swellable layer constituted by high viscosity cellulose derivatives of high molecular weight. Drug release in this system is dependent upon the pH to which the formulation is exposed. The inner layer is a polymer which is soluble only at a pH value of 7 or higher, and this layer must be dissolved before the release of mesalamine can begin.

Accordingly, there remains a continuing need in the art for pharmaceutical formulations which release active ingredient at a predetermined site or location in the body after a predetermined latency or lag time period, i.e., site-specific release formulations. In particular, there remains a need in the art for a pharmaceutical formulation for the site-specific delivery of mesalamine which achieves effective release of mesalamine directly into the colon. There further remains a need in the art for a method of preparing a pharmaceutical formulation for the site-specific delivery of mesalamine which does not require the use of organic solvents, or very dilute solutions of coating materials.

Summary of the Invention

It is therefore an object of the present invention to provide a pharmaceutical formulation for the site-specific delivery of mesalamine. It is a further object of the present invention to provide a site-specific, controlled

release pharmaceutical formulation for mesalamine which provides release of mesalamine from the formulation at the predetermined site of delivery.

As a first aspect, the present invention provides a pharmaceutical formulation for the site-specific delivery of mesalamine in the colon. The formulation comprises: *a*) a core comprising mesalamine in an amount effective to produce a therapeutic anti-inflammatory effect; *b*) a swellable polymeric coating layer substantially surrounding the core which inhibits the release of mesalamine for a predetermined period of time dependent upon the thickness of the swellable polymeric coating layer; and *c*) an outer enteric coating layer substantially surrounding the swellable polymeric coating layer. The outer enteric coating layer inhibits the swelling of the swellable, intermediate coating layer until the formulation reaches the duodenum and dissolves upon exposure to pH above 4.5. The dissolution, erosion or disintegration of the outer enteric coating layer triggers the subsequent swelling and dissolution of the swellable polymeric coating layer.

As a second aspect, the present invention provides a method for achieving the site-specific delivery of mesalamine in the colon of a subject in need of such treatment. The method comprises orally administering to a subject in need thereof, a site-specific dosage formulation including: *a*) a core comprising mesalamine in an amount effective to produce a therapeutic anti-inflammatory effect; *b*) a swellable polymeric coating layer substantially surrounding the core, wherein the swellable polymeric coating layer inhibits the release of mesalamine for a predetermined period of time dependent upon the thickness of the swellable polymeric coating layer; and *c*) an outer enteric coating layer substantially surrounding the swellable polymeric coating layer, wherein the outer enteric coating dissolves upon exposure to pH greater than about 4.5, and wherein the dissolution of the outer enteric coating layer initiates the swelling and dissolution of the swellable polymeric coating layer.

The foregoing and other objects and aspects of the present invention are explained in detail in the detailed description and examples set forth hereinbelow.

Detailed Description of the Invention

The pharmaceutical formulations and methods of the present invention provide a site-specific controlled-release pharmaceutical formulation for mesalamine and other nonsteroidal anti-inflammatory drugs which are desireously delivered in a site-specific manner to the colon.

Generally, the pharmaceutical formulations of the present invention include a core, a swellable polymeric coating layer and an outer enteric coating layer which dissolves upon exposure to a pH greater than about 4.5.

The core is comprised of the active ingredient, i.e., mesalamine. In addition, the core typically also includes one or more pharmaceutically acceptable excipients. Pharmaceutically acceptable excipients which may be employed are well known to those skilled in the art and include any conventional pharmaceutically acceptable tableting excipients. Examples of suitable excipients which may be included in the core of the formulations of the present invention include but are not limited to microcrystalline cellulose, dibasic calcium phosphate dihydrate, starch, magnesium stearate, lactose, colloidal silicon dioxide, talc, and glyceryl behenate.

The core can be prepared by any suitable tableting technique known to those skilled in the art. For example, the active ingredient may be admixed with the excipient(s) and advantageously formed into a tablet using a conventional tableting press. Alternatively, the core may be formulated as capsules, soft capsules, mini-tablets, granules, pellets, or spheronized crystals if desired, using conventional techniques.

In order to achieve the site-specific pharmaceutical formulation. the core is coated with an intermediate layer which is a swellable polymeric coating layer. The swellable polymeric coating layer delays the release of

mesalamine for a predetermined period of time, which period of time is dependent upon the thickness of the swellable polymeric coating. In other words, the thicker the swellable polymeric coating, the longer it delays the release of the active ingredient from the core of the formulation. Thus, the appropriate site for the release of the active ingredient can be determined prior to the preparation of the formulation, and the formulation is designed by applying the appropriate thickness of swellable polymeric coating layer to achieve the desired time delay required to reach the predetermined site of delivery prior to release of the active ingredient.

The site-specific delivery of mesalamine using the instant formulation relies in part upon the fact that the residency time in the small intestine is relatively uniform from patient to patient. Typically, the transit time in the small intestine is 3 ± 1 hours according to S. Davis et al., *Gut* **27**:886 (1986). The formulation of the present invention relies upon the use of a control mechanism which can recognize the entry into the small intestine, and the use of polymer(s) or copolymer(s) which prevent the release of mesalamine from the core for the time needed to pass through the small intestine segment of the digestive tract.

The swellable polymeric coating layer comprises a hydrophilic gelling polymer or copolymer that swells on contact with gastro-intestinal juices to form a film surrounding the core. The swellable polymeric coating layer which surrounds the core protects the integrity of the core and prevents the release of mesalamine during the transit in the small intestine.

The swellable polymeric coating layer may be comprised of any suitable hydrophilic gelling polymer known to those skilled in the art. For example, suitable hydrophilic gelling polymers include but are not limited to cellulose polymers such as methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, and the like, vinyl polymers such as polyvinylpyrrolidone, polyvinyl alcohol, and the like, acrylic polymers and copolymers such as acrylic acid polymer,

methyacrylic acid copolymers, ethyl acrylate-methyl methacrylate copolymers, and the like; natural or synthetic rubbers, poloxamers, polysaccharides, and mixtures thereof. Currently the preferred swellable polymeric coating layer comprises hydroxypropylmethylcellulose.

Hydroxypropylmethylcellulose is a polymer which is available in many grades, including types of different weight average molecular weight, extremely different viscosity, and different substitution grade. In one preferred embodiment, the swellable polymeric coating layer comprises a relatively low viscosity hydroxypropylmethylcellulose polymer having 1) a typical weight percent substitution corresponding to 29% methoxyl and 8% hydroxypropoxyl groups, and 2) a nominal viscosity of a 2% watery solution at 20°C ranging from 3 to 100 mPa.s, such as METHOCEL E5®, METHOCEL E50®, OR METHOCEL E100®, all available from Colorcon or PHARMACOAT 603® available from Seppic.

In addition to the foregoing, the swellable polymeric coating layer may also include additional excipients such as plasticizers, antisticking agents, and colorants. Specific examples of additional excipients include polyethylene glycol, polyvinylpyrrolidone, talc, magnesium stearate, glyceryl behenate, stearic acid, and titanium dioxide.

The swellable polymeric coating layer may be applied to the core using conventional film (or spray) coating techniques or double press coating. Preferably, the swellable polymeric coating layer is applied using the film coating techniques whereby the polymer is solubilized in an aqueous solution. Typically, the polymer used for film coating exhibits a viscosity ranging from about 3 to 100 mPa.s at 25°C in a 2% aqueous solution. Higher viscosity polymers can be applied using organic solutions or double press coating. Although some organic solvents may be employed in the film coating application of the swellable polymeric coating layer, the inclusion of organic solvents in the film coating solution is not required.

The solution of swellable polymer can be applied to the core by any means of film coating including but not limited to fluid bed, and pan coating. Preferably, the aqueous solution swellable polymer is sprayed on the core to form the swellable polymeric coating layer.

The swellable polymer is applied to the core (preferably by fim-coating) in order to build the desired thickness of the swellable polymeric coating layer. For example, in the embodiment wherein film coating is employed, the core is sprayed with the solution of polymer until the desired thickness of swellable polymeric coating layer is achieved. The desired thickness of the swellable polymeric coating layer is dependent upon the desired delivery site of the active ingredient. The thicker the swellable polymeric coating layer around the core, the longer the latency, or lag time prior to delivery of the mesalamine, and thus the farther through the gastro-intestinal tract the mesalamine will be delivered. Typically, the swellable polymeric coating layer is applied to a thickness sufficient to achieve a weight gain of between about 5 and about 200 percent, preferably between about 10 and about 100 percent as determined by solid substance. The weight ratio of the core:swellable polymeric coating layer is typically between about 20:1 and about 1:5, providing a thickness of swellable polymeric coating layer in excess of about 30 μm, and up to about 3 mm. Preferably the ratio of core:swellable polymeric coating layer is between about 5:1 and about 1:3 inclusive, or a thickness of between about 100 μm and about 1600 μm.

The dissolution, disintegration, or erosion of the swellable polymeric coating layer at the desired site of delivery is triggered by the dissolution, erosion, or disintegration of the outer gastro-resistant layer. Once the predetermined delivery site is reached and the outer coating layer is dissolved, the swellable polymeric coating layer should be capable of relatively quick swelling and dissolution. The use of the low viscosity cellulose polymers for the preparation of the swellable polymeric coating layer according to the present invention provides a distinct advantage in this respect. The low viscosity

cellulose polymers which are used according to the present invention are characterized by a quicker solubilization, dissolution, or erosion time as compared to the high viscosity polymers. This relatively quick erosion time facilitates the maintenance of thinner levels of a thin swollen polymeric layer which is generated upon hydration. In other words, the erosion of the swollen polymeric coating layer proceeds uniformly. The achievement of a thin swollen layer permits a higher speed of release of mesalamine once the swellable polymeric coating layer has completely interacted and dissolved. The quick release of mesalamine provides a complete availability of the drug at the desired site of delivery.

The outer enteric coating layer of the instant formulation is a gastro-resistant coating layer, which permits the transit of the intact formulation through the stomach until the duodenum is reached. The outer coating layer overlies the swellable polymeric coating layer.

The outer enteric coating layer is comprised of conventional gastro-resistant polymers. For example, suitable gastro-resistant polymer for the outer enteric coating layer include acrylic/methacrylic copolymers, polyacrylates, polymethacrylates, acetate-phthalate cellulose, cellulose acetate terephthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, or polyvinyl alcohol phthalate. Preferably, the outer enteric coating layer comprises acrylic/methacrylic copolymers such as those commercially available under the trade name EUDRAGIT®.

The outer enteric coating layer comprising the gastro-resistant polymer preserves the integrity of the formulation and inhibits the start of the swelling of the swellable polymeric coating layer during the gastric transit. The dissolution of the outer enteric coating layer is triggered by the presence of gastro-intestinal media having a pH above about 4.5, such as that present in the small intestine. Preferably, the dissolution of the outer enteric coating layer occurs when the formulation is subjected to a pH above about 5, and often above about 5.5. The dissolution of the outer enteric coating layer initiates the swelling

of the swellable polymeric coating layer. Thus, once the outer enteric coating layer is dissolved, the swelling, dissolution, and erosion of the swellable polymeric coating layer begins. The dissolution, erosion, or disintegration of the swellable polymeric coating layer inhibits the release of active ingredient from the core until the desired site of delivery is reached.

The outer enteric coating layer may be applied using any conventional coating techniques, including for example film coating techniques as described above. Preferably, the core coated with the swellable polymeric coating layer is further coated with the outer enteric coating layer using conventional spray coating techniques, wherein the coating process is carried out with a solution or suspension containing the gastro-resistant polymer which forms the outer enteric coating layer agent solubilized or suspended in a suitable solvent. Solvents useful for preparing the solution containing the outer coating agent include any pharmaceutically acceptable solvents capable of solubilizing the selected outer coating agent. A preferred solvent for preparing the solution containing the outer coating agent is water.

The site-specific dosage formulation of the present invention is suitable for oral administration and delivery in the colon. In order to achieve the site-specific delivery of mesalamine or other anti-inflammatory active ingredient, one need only administer the site specific formulation of the present invention to a subject in need of the a therapeutically effective dose of anti-inflammatory in the colon. Subjects in need of such treatment include humans, particularly humans suffering from ulcerative colitis or other inflammatory bowel disorders.

The formulation of the present invention provides a number of distinct advantages over conventional mesalamine formulations. As noted above, the formulation of the present invention utilizes often low viscosity cellulose polymers as the swellable polymeric coating layer, thus avoiding the necessity of including an organic solvent in the film coating process. Also, the low viscosity cellulose polymers permit the quick release of mesalamine at the pre-determined site. In addition, the formulation of the present invention provides the further

advantage that the release pattern of mesalamine after the dissolution of the outer enteric coating layer is not dependent upon or controlled by pH.

The following examples are provided to illustrate the present invention, and should not be construed as limiting thereof. In these examples, "mg" means milligrams, "g" means grams, "mm" means millimeters, "μm" means micrometers, "kp" means 9.807 Newton, "min." means minute(s), and "°C" means degrees Centigrade. All percentages are in percent by weight of the tablet unless otherwise indicated. Dissolution/disintegration tests are carried out according to the standard procedures set forth in the United States Pharmacopoeia for testing the dissolution/disintegration of tablets.

EXAMPLE 1

Tablet cores (20,000) containing 400 mg of mesalamine are prepared with the following composition:

Mesalamine	400	mg
Lactose	57	mg
Crospovidone	20 mg	
Talc	8	mg
Glyceryl behenate	8	mg
Polyvinylpyrrolidone	7	mg

Mesalamine is granulated with 10% solution of polyvinylpyrrolidone in order to obtain a homogeneous granulate. Thereafter, the wet mass is sieved and dried at 40°C for 6 hours. The dried granules are calibrated through an adapted screen and then mixed with crospovidone, lactose, talc, and glycerol behenate in a ribbon mixer. The granular mixture is formed into tablet cores of 10mm in diameter, weighing 500 mg each using a rotary tablet press. The cores show a disintegration time lower than 5 minutes in water, a Schleuninger hardness higher than 10 kp and a friability lower than 0.1%.

The inner layer is applied onto the tablet cores in an automatic coating pan using the following solution:

Hydroxypropylmethycellulose (Methocel E50®)	7.5% w/w
PEG 6000	1.5% w/w
Water	91.0% w/w

Samples having a weight gain included from 10% to 50% are of the core weight are collected for analysis.

The results obtained are summarized in the following table:

	Weight (n=30±S.D.)	Tablet height (n=30±S.D.)	Layer Thickness (microns)
Uncoated Core	507.6±44.5	6.595±0.051	
+10%	558.2±10.3	6.998±0.078	200
+20%	610.4±13.6	7.368±0.081	385
+30%	662.2±12.1	7.676±0.081	540
+40%	711.6±15.8	7.951±0.094	680
+50%	767.0±13.6	8.275±0.068	840

Subsequently the outer layer is applied by continuous spraying of an aqueous gastroresistant suspension of CAP (Cellulose Acetate Phthalate), containing triacetin as plasticizer.

The disintegration test carried out on the finished tablets shows the absence of release at pH lower than 5 for at least 2 hours. Upon increasing the pH of the medium up to 7.5 the disintegration of the tablets occurs in 256 ± 10.8 minutes.

EXAMPLE 2

Tablet cores containing 400 mg of mesalamine are prepared as described in the example 1, and press-coated with a mixture of hydroxypropylmethylcellulose (Methocel E50™, available from Colorcon), polyvinylpyrrolidone and polyethylenglycol, in the ratio 7:2:1, by means of a press-coating machine, to obtain a press-coated tablet having a weight of 800 mg.

The tablets are coated by a continuous spraying of a gastroresistant film of methacrylic ester aqueous suspension using an automatic pan.

EXAMPLE 3

The site-specific dosage formulation of the present invention allows the release of mesalamine after the arrival of the formulation in the large bowel (ascending colon, transverse colon and descending colon). This phenomenon was observed by scintigraphic imaging in human volunteers orally dosed with tablet containing mesalamine formulated according to the present invention and labeled with ^{153}Samarium. This result suggests that this technology increases the topical therapeutic effect of mesalamine while reducing the systemic absorption. The reduced systemic absorption of mesalamine is well documented by the much lower blood peak concentration of mesalamine (about 10-fold lower than a conventional formulation) and percentage of urinary excretion of the metabolite n-acetylmesalamine (6% vs 19-30% of conventional formulation) which is a marker of systemic absorption.

The foregoing is illustrative of the present invention and is not to be construed as limiting thereof. The invention is defined by the following claims, with equivalents of the claims to be included therein.

That Which Is Claimed Is:

1. A pharmaceutical formulation for the site-specific delivery of mesalamine in the colon, said formulation comprising:

a) a core comprising mesalamine in an amount effective to produce a therapeutic anti-inflammatory effect;

b) a swellable polymeric coating layer substantially surrounding said core, wherein said swellable polymeric coating layer inhibits the release of said mesalamine for a predetermined period of time dependent upon the thickness of said swellable polymeric coating layer, and wherein dissolution of said swellable polymeric coating layer is independent of pH to which said swellable polymeric coating layer is exposed; and

c) an outer enteric coating layer substantially surrounding said swellable polymeric coating layer, wherein said outer enteric coating layer dissolves upon exposure to pH greater than about 4.5, and wherein the dissolution of the outer enteric coating layer initiates the subsequent swelling of the swellable polymeric coating layer.

2. The pharmaceutical formulation according to Claim 1, wherein said core further comprises at least one pharmaceutically acceptable excipient.

3. The pharmaceutical formulation according to Claim 1, wherein said swellable polymeric coating layer comprises a hydrophilic gelling polymer selected from the group consisting of methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, acrylic acid polymer, methacrylic acid copolymers, ethyl acrylate-methyl methacrylate copolymers, natural rubbers, synthetic rubbers, poloxamers, polysaccharides, and mixtures thereof.

4. The pharmaceutical formulation according to Claim 1, wherein said swellable polymeric coating layer is sufficiently thick to achieve a weight gain based upon the weight of the core of between about 5 and 200 percent.

5. The pharmaceutical formulation according to Claim 1, wherein said swellable polymeric coating layer is not less than about 30 μm thick.

6. The pharmaceutical formulation according to Claim 1, wherein said swellable polymeric coating layer is between about 30 μm and about 3 mm thick.

7. The pharmaceutical formulation according to Claim 1, wherein said swellable polymeric coating layer comprising hydroxypropylmethylcellulose.

8. The pharmaceutical formulation according to Claim 1, wherein said enteric coating layer comprises a gastro-resistant polymer selected from the group consisting of acrylic/methacrylic copolymers, polyacrylates, polymethacrylates, acetate-phthalate cellulose, cellulose acetate terephthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, or polyvinyl alcohol phthalate.

9. A method for achieving the site-specific delivery of mesalamine in the colon of a subject in need of such treatment, said method comprising orally administering to said subject, a site-specific dosage formulation comprising *a*) a core comprising mesalamine in an amount effective to produce a therapeutic anti-inflammatory effect, *b*) a swellable polymeric coating layer substantially surrounding said core, wherein said swellable polymeric coating

layer inhibits the release of mesalamine for a predetermined period of time dependent upon the thickness of said swellable polymeric coating layer, and wherein dissolution of said swellable polymeric coating layer is independent of pH to which said swellable polymeric coating layer is exposed; and *c*) an outer enteric coating layer substantially surrounding said swellable polymeric coating layer, wherein said outer enteric coating dissolves upon exposure to pH greater than about 4.5, and wherein the dissolution of said outer enteric coating layer initiates the swelling of said swellable polymeric coating layer.

10. The method according to Claim 9, wherein said core further comprises at least one pharmaceutically acceptable excipient.

11. The method according to Claim 9, wherein said swellable polymeric coating layer comprises hydrophilic polymer selected from the group consisting of methylcellulose, carboxymethylcellulose, hydroxypropylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, acrylic acid polymer, methacrylic acid copolymers, ethyl acrylate-methyl methacrylate copolymers, natural or synthetic rubbers, poloxamers, polysaccharides, and mixtures thereof.

12. The method according to Claim 9, wherein said swellable polymeric coating layer is sufficiently thick to achieve a weight gain based upon the weight of the core of between about 5 and 200 percent.

13. The method according to Claim 9, wherein said swellable polymeric coating layer is not less than about 30 μm thick.

14. The method according to Claim 9, wherein said swellable polymeric coating layer is between about 30 μm and about 3 mm thick.

15. The method according to Claim 9, wherein said swellable polymeric coating layer comprising hydroxypropylmethylcellulose.

16. The method according to Claim 9, wherein said enteric coating layer comprises a gastro-resistant polymer selected from the group consisting of acrylic/methacrylic copolymers, polyacrylates, polymethacrylates, acetate-phthalate cellulose, cellulose acetate terephthalate, cellulose acetate trimellitate, hydroxypropylmethylcellulose phthalate, or polyvinyl alcohol phthalate.